Docket No.: ARC 2399
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Patent Application of:<br>Joseph B. Phipps | : |
| Application No.: 08/463,904 | : Group Art Unit: 3762<br>: Examiner: M. Bockelman |
| Filed: June 5, 1995 | : |
| For: METHOD AND DEVICE FOR TRANSDERMAL ELECTROTRANSPORT DELIVERY OF FENTANYL AND SUFENTANIL | : |

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**Commissioner for Patents**
**P.O. Box 1450**
**Alexandria, VA 22313-1450**

**REPLY BRIEF**

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## Status of Claims

Claims 1, 4 and 7-9 are presently on appeal.

## Grounds of Rejection to be Reviewed on Appeal

1. Whether claims 1, 4 and 7-9 are properly rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Phipps, et al., U.S. Patent No. 5,423,739 (hereafter the '739 patent), an excerpt from a Russian text by Rebinder (hereafter Rebinder), Phipps et al. U.S. Patent No. 5,125,894 (hereafter the '894 patent), and Muller et al. U.S. Patent No. 5,320,731 (hereafter the Muller et al. or the '731 patent).

2. Whether claims 1, 4 and 7-9 are properly rejected under 35 U.S.C. § 102(b) as being anticipated by Haak, et al. U.S. Patent No. 5,203,768 (hereafter Haak, et al. or the '768 patent), and whether the claims have been properly rejected under 35 U.S.C. § 103 as being unpatentable over the combination Haak, et al. in view of Rebinder, the '894 patent and Muller, et al. or in view of Newman, U.S. Patent No. 4,931,046 (hereafter Newman or the '046 patent).

3. Whether claims 1, 4 and 7-9 are properly rejected under 35 U.S.C. § 102(b) as being anticipated by the claims of Theeuwes, et al., U.S. Patent No. 5,332,438 (hereafter Theeuwes et al. or the '438 patent), and whether the claims have been properly rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Theeuwes, et al. in view of Rebinder, the '894 patent and Muller, et al. or in view of Newman.

4. Whether claims 1, 4 and 7-9 have properly been rejected on "obviousness-type" double patenting grounds over the claims of United States Patent No. 6,171,294 (hereafter the '294 patent).

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## Argument

Appellant respectfully submits that the Examiner has failed to establish the requirements of a *prima facie* case of anticipation, obviousness or obviousness-type double patenting. In this regard, it is important to note that none of the references relied upon by the Examiner teaches or suggests the specifically claimed range. The claims in the instant application pertain to an unpredictable area in which many variables affect the iontophoretic flux of the drug. In this regard, the predecessor court to the Federal Circuit has stated that "logic and reason compel the conclusion that in an area of technology shown to be highly unpredictable in process values, the discovery of optimum values not in any way suggested by the prior art is more likely to be unobvious than obvious within the meaning of § 103." *In re Sebek*, 465 F.2d 904, 907, 175 USPQ 93, 95 (CCPA 1972). The Examiner's Answer characterizes the pending claims as "involving nothing more than a routine testing to determine the molarity at which Fentanyl should be maintained during delivery so as to maintain a linear relationship between flux and current". The Examiner is incorrect.

Instead of relying on facts and the teachings of the references, the Examiner appears to base the rejections on the opinion that the invention is based on routine testing, doubts about the statements made in two affidavits submitted by the inventor, and hindsight reconstruction of the claimed invention. Appellant respectfully submits that rejections based on "allegations regarding a 'common, routine expedient,' the 'expected skill of the art to determine optimum proportions' or the belief 'that workers in the art would recognize that * * * values * * * are rarely the same,'" however true as they may

be, when unsupported by sufficient facts, are insufficient to maintain a *prima facie* case of obviousness. *In re DeJong*, 416 F.2d 1401, 1404-05, 163 U.S.P.Q. 479 (CCPA 1969).

The Examiner is unwilling to accept the factual evidence submitted in two affidavits by Dr. Phipps, who has conducted research and development in the field of iontophoresis since 1983, is a named inventor on 30 patents and an author on 30 articles and book chapters on iontophoresis, is an internationally recognized expert in the field of transdermal iontophoretic drug delivery and has been invited to present his research at numerous scientific conferences and workshops, including the Gordon Research Conference, Solid State Ionics meeting, and the annual conferences of the Controlled Release Society and The Electrochemical Society. The evidence contained in the declarations based on the statements of Dr. Phipps and supported by numerous articles, has not changed since they were submitted in 1997 and 1998. The Examiner's rejections are based on the Examiner's doubt that the invention is patentable and unfounded assumptions and speculation about the theory of iontophoresis, largely due to doubts about the role of extraneous ions. It is well established that in making rejections over the prior art, the Patent Office "may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis." *In re Warner*, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), *cert. denied*, 389 U.S. 1057, 19 L. Ed. 2d 857, 88 S. Ct. 811 (1968).

The Examiner's Answer, submitted over two years after Appellant's Amended Brief on Appeal was filed, is 42 pages long and contains numerous inaccurate statements pertaining to the invention, the prior art and the affidavits submitted during prosecution

of this application. Many of the issues raised in the Examiner's Answer will not be directly addressed in this Reply Brief, and appellant respectfully refers the Board to the Amended Brief on Appeal and the articles and affidavits appended to the Amended Brief on Appeal. A request for Oral Hearing has been separately submitted, and any issues pertinent to the patentability of the pending claims or questions raised by the Examiner's Answer can be addressed by Appellant at the Oral Hearing.

The Summary of Claimed Subject Matter contains misstatements and misunderstandings about the claimed invention. In particular, the claimed invention delivers fentanyl ions, not fentanyl salt as stated by the Examiner. In addition, contrary to the statement made on page 3 of the Examiner's Answer, the point at which normalized flux approaches 100% is not dependent on ions in solution, as was amply explained in the second Phipps declaration, the Amended Brief on Appeal and as will be explained further below.

The remainder of this Reply Brief addresses selected points in the Response to Arguments section starting on page 17 of the Examiner's Answer and follows the outline format presented in the Response to Arguments Section Examiner's Answer.

1. Rebuttal to Arguments/Evidence/Affidavits presented in the Appeal Brief

A. Background-Toxicity Arguments

Regarding the position advanced starting on page 17 of the Examiner's Answer, Yerasi and Edinboro are relied upon for the simple concept that fentanyl, regardless of the form of the drug (salt or free base), is a highly potent opioid, and as such, it would not be desired to have an amount remaining in an electrotransport device after the device has

been used. Any amount of opioid remaining in a device presents danger of abuse by a person accessing the remaining amount and misusing the opioid.

The quotation of U.S. Patent No. 4,588,580 (hereafter the '580 patent) on page 3 of the Appeal Brief and cited by the Examiner, acknowledges the fact that fentanyl and its derivatives have a high potential for abuse and that it is desired to keep "the amount of drug within the unused and depleted systems to a minimum." The Yerasi and Edinboro articles and the '580 patent cited in the Appeal Brief amply establish the desire in the art to minimize the amount of fentanyl and fentanyl salts in electrotransport devices and to minimize the amount of unused fentanyl in such systems.

The discussion of the '580 patent, particularly the interpretation of the passage of the '580 patent at col. 7, lines 65+ on page 21 of the Examiner's Answer, misinterprets the teachings of the '580 patent. The passage cited by the Examiner (Example 1) teaches an example of a system in which excessive residual drug is left in the reservoir after use, and the remaining Examples teach improved results over Example 1. The '580 patent teaches the desire to minimize the amount of drug remaining in the reservoir after use (col. 2, lines 24-27), and Example 3 describes the improved results in that less residual drug is left in the reservoir as compared to Example 1 (col. 8, lines 18-37).

Similarly, the reliance on Lattin et al. United States Patent No. 5,879,322 (the '322 patent) in the Examiner's Answer (at page 21) is also unavailing, as this patent deals with the problem of inadvertent contact with iontophoresis devices. In the '322 patent, one of the goals of the patent is to minimize the contact of the drug reservoirs with the skin of the persons disposing of the device. Applicant does not dispute that some drug

remains after use in the reservoir of electrotransport devices described in the '322 patent. The '322 patent teaches one of many ways to prevent inadvertent contact with the drug.

C. The Phipps Declarations

The two declarations by Dr. Joseph B. Phipps, the inventor, are described in the Appeal Brief and attached in Appendix D of the Amended Brief on Appeal. Both declarations provide facts and supporting technical articles explaining how the claimed invention proceeded contrary to the teachings in the art.

The Examiner's Answer contains numerous incorrect and inaccurate statements with respect to both of the Phipps declarations, many of which are irrelevant to the patentability of the claimed invention and which are not addressed in this Reply Brief. The first Phipps declaration states that in passive delivery systems, it is desired to that the donor reservoir contain only the amount of drug needed for treatment of the patient to minimize the potential for inadvertent misuse or abuse of a "used" system. This fact is supported by the Yerasi et al. article, cited in the Appeal Brief at page 3 and which describes the misuse of used fentanyl patches containing residual fentanyl. The first declaration also discusses the Padmanabhan et al. article, which teaches that the delivery rate of hydromorphone hydrochloride an opioid similar to fentanyl, is independent of the concentration of the hydromorphone in the donor solution over a wide range and below 1 millimolar. The declaration also discusses the Kasting and Keister article, which teaches that the theoretical efficiency of drug delivery in salt form is independent of drug concentration. The first declaration concludes with a statement that the claimed invention proceeds against the teachings of the art to minimize the amount of unused fentanyl in a used device and to maintain a surprisingly high concentration of fentanyl in

the donor reservoir throughout the entire delivery period of the device, resulting in a substantial amount of fentanyl in the used device to avoid a concentration of drug dependent on flux.

Contrary to the assertions in the Examiner's Answer, hydromorphone is not completely unrelated in structure and molecular weight to fentanyl. First, both fentanyl and hydromorphone are mu-opioid agonists and therefore have distinct structural similarities necessary to bind to the mu receptor. Both fentanyl and hydromorphone form water soluble positive ions over a similar pH range with a charge of +1. Moreover, the molecular weight of fentanyl is 336.476, and the molecular weight of hydromorphone is 285.341, which are relatively similar. And most importantly, the transport number of each ion through human skin is about 0.1 (*i.e*, one tenth of the ionic current passing through the skin is due to the drug ion). A similar transport number strongly indicates that the transport mechanism of each ion through the skin is the same. This is as expected since the skin pathway for organic ions consists of aqueous regions associated with sweat glands and hair follicles. These facts were well-documented in the literature at the time of the invention. Based on these facts, there was ample rationale to expect similar transport results and therefore similar dependence on drug concentration. The Examiner's Answer does not provide any evidence for the unsupported allegations in the Answer concerning hydromorphone and fentanyl, particularly that the "[t]here are no parallels in expectations."

The second Phipps declaration addresses the Examiner's understanding of the prior art and technically incorrect statements made by the Examiner during prosecution of the application. In particular, the second Phipps declaration discusses the teachings of

United States Patent No. 5,125,894 and explains that the first declaration discussed the Padmanabhan article because the Padmanabhan article is the source of a statement in the '894 patent relied upon by the Examiner in rejecting the claims. The second Phipps declaration also explains role of extraneous ions and further explains why the cited prior art does not teach the claimed invention.

2. Examiner's Rebuttal to Arguments/Evidence/Affidavits presented in Appeal Brief

None of the cited references, alone or in combination, teach or suggest the claimed invention. As argued in the Amended Brief on Appeal, the references relied upon by the Examiner present an "obvious-to-try" situation.

Regarding the alleged "new approach" to "parasitic ions" referred to in the Examiner's Answer at page 30, this was addressed in the Amendment submitted on February 27, 2002 at page 5. It is well known in the art of iontophoresis that as the iontophoretic flux of a drug decreases, a greater portion of electrotransport current is carried by chloride ions migrating from the other side of the epidermis, and not due to the presence of extraneous ions as stated by the examiner. This fact is supported by an article authored by the inventor and two co-authors, who have authored numerous papers and are named inventors on several patents in the area of iontophoresis, in a peer-reviewed article published in the Journal of Pharmaceutical Sciences in May of 1989, which is part of the record in this application. At page 367 of this article, which has been submitted as a reference in an Information Disclosure in the instant application, the authors' state:

> "The efficiency of drug delivery is primarily determined by the following two factors: the extraneous ion concentration in the donor

> reservoir, and the mobility...of the drug ion in the skin relative to that of other ions migrating through the skin (e.g., chloride ions). The extraneous ion concentration in the donor reservoir should be minimized in order to maximize the delivery efficiency." (emphasis supplied)

The examiner has focused on the role of the extraneous ions (*i.e.*, non-drug ions in the drug reservoir) in making his counter arguments. Appellant respectfully submits that this point on the important role of chloride ions in the skin and their competitive transport mechanism is misunderstood by the Examiner, and it is commonly misunderstood by others. Appellant reiterates the simple fact that the drop off in delivery cannot be due to extraneous ions since the quantity of extraneous ions in reservoir is exceedingly small when the delivery of fentanyl decreases below 16 mM. The examiner's extensive arguments about extraneous ions and the science of drug transport are factually incorrect and not germane to question of patentability.

The arguments advanced on pages 31-35 of the Examiner's Answer, contain numerous misinterpretations of the invention and the science of iontophoresis and are based on unfounded assumption, particularly those pertaining to competitive ions and silver anodes. For example, page 35 of the Examiner's Answer contains the statement: "Because the linear relationship between current and quantity of drug delivered is so critical to be maintained so as to know the amounts delivered..." This linear relationship has been relied upon in rejection of the claims many times, but there is no requirement in the claimed invention that this relationship be maintained. The claimed invention can be practiced whether this linear relationship is maintained or not. The claimed invention is focused on a method of drug delivery with a lack of dependence of flux on drug concentration, not this linear relationship.

The Examiner maintains the obviousness-type double patenting rejection over the Southam patent, on the basis that Southam claims are "another manner of claiming the same invention of treating a patient with fentanyl salt for pain." In addition, the Examiner states that "There is substantial overlap in the method and one would preclude the other." (Examiner's Answer at page 36.) The Examiner attempts to support this rejection with the rationale that 100 equal dosages are delivered and that the patch must contain a fentanyl salt concentration of 16 mM during each of the time periods of delivery. Examiner's Answer at page 17.)

The Amended Brief on Appeal makes clear that the Examiner has failed establish a case of obviousness-type double patenting. Like the obviousness rejections, the Examiner relies on unsupported assumptions about the claims of Southam in making obviousness-type double patenting rejection. First, the Southam claims pertain to a dosing regimen for treating pain. The Southam claims do not recite the volume of gel present or any information that would allow one to calculate the volume of gel. Thus, there is no indication of the residual level of fentanyl in the donor reservoir in the claims of the Southam patent, and this residual level cannot be gleaned from the percentage recited in claim 7 of Southam. The Examiner relies on unsupported assumptions to arrive at an obvious to try standard in rejecting the claims for obviousness type double patenting, which is improper. "[A] double patenting of the obvious type rejection is 'analogous to [a failure to meet] the non-obviousness requirement of 35 USC § 103,' except that the patent principally underlying the double patenting rejection is not considered prior art." *In re Longi*, 759 F.2d 887, 892 n.4 (Fed. Cir. 1985). The Examiner

has failed to establish that the claims are not patentably distinct, and as such, the Examiner has failed to establish a case of obviousness-type double patenting.

As noted above, the claims in the instant application pertain to an unpredictable area in which many variables affect the iontophoretic flux of the drug. Appellant discovered that contrary to the teachings of the art at the time of the invention, concentration, except at extremely low levels orders of magnitude below the range recited in the claims, was believed to be a variable that did not affect iontophoretic flux. Also, it is generally desirable to minimize the amount of unused opioid in the device after use, a high concentration of fentanyl is required to achieve a constant iontophoretic flux during the entire drug delivery period. Appellant's discovery was surprising in view of the teachings in the literature.

The fact that the claimed fentanyl concentration is far outside any range taught or suggested by the prior art militates against the Examiner's conclusion that optimization of this parameter would result in the Appellant's claimed values. See *In re Sebek*, 465 F.2d at 907, 175 USPQ at 95. Instead, Appellant submits that the rejections of the instant claims are based on improper speculation, unfounded assumptions or hindsight reconstruction.

**Conclusion**

In view of the foregoing and particularly for the reasons set forth in the Amended Brief on Appeal, appellant submits that claims 1, 4 and 7-9 of the application are patentable over the references of record. Appellant respectfully submits that the art of record does not anticipate, render obvious or presents an obviousness-type double patenting situation.

Additionally, for the reasons set forth in the Amended Brief on Appeal, claim 9 is separately patentable over the documents of record. Accordingly, appellants respectfully request reversal of each of the rejections on appeal.

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Respectfully submitted,

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